PROCESS FOR PREPARING INTERMEDIATES USEFUL TO PREPARE CERTAIN ANTIBACTERIAL N-FORMYL HYDROXYLAMINES.

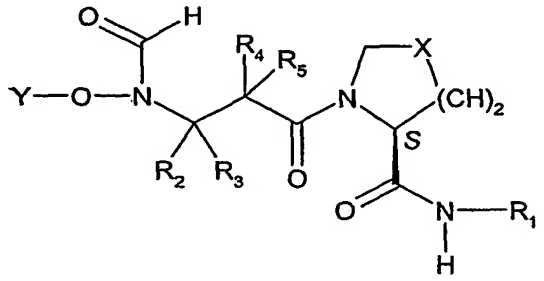
This invention is directed to a process for preparing intermediates that are useful to prepare certain antibacterial *N*-formyl hydroxylamine compounds.

Peptide deformylase is a metallopeptidase found in prokaryotic organisms such as bacteria. Protein synthesis in prokaryotic organisms begins with *N*-formyl methionine (fMet). After initiation of protein synthesis, the formyl group is removed by the enzyme peptide deformylase (PDF); this activity is essential for maturation of proteins. It has been shown that PDF is required for bacterial growth. See Chang et al., *J. Bacteriol.*, Vol. 171, pp. 4071-4072 (1989); Meinnel et al., *J. Bacteriol.*, Vol. 176, No. 23, pp. 7387-7390 (1994); Mazel et al., *EMBO J.*, Vol. 13, No. 4, pp. 914-923 (1994). Since protein synthesis in eukaryotic organisms does not depend on fMet for initiation, agents that will inhibit PDF are attractive candidates for development of new anti-microbial and anti-bacterial drugs.

Co-pending Application Serial No. 10/171,706, filed June 14, 2002 (incorporated herein by reference in its entirety), PCT equivalent published as WO 02/102790 A1, discloses novel *N*-formyl hydroxylamine compounds that inhibit PDF and are therefore useful as antibacterial agents. The compounds disclosed therein are certain *N*-[1-oxo-2-alkyl-3-(*N*-hydroxyformamido)-propyl]-(carbonylamino-aryl or -heteroaryl)-azacyclo$_{4-7}$alkanes or thiazacyclo$_{4-7}$alkanes which are described in more detail hereinafter. An improved process has been discovered for preparing intermediates useful for preparing these *N*-[1-oxo-2-alkyl-3-(*N*-hydroxyformamido)-propyl]-(carbonylamino-aryl or -heteroaryl)-azacyclo$_{4-7}$alkanes or thiazacyclo$_{4-7}$alkanes.

The present invention is directed to a novel process for preparing certain intermediates which are useful to prepare certain *N*-formyl hydroxylamine compounds which are useful for inhibiting bacteria.

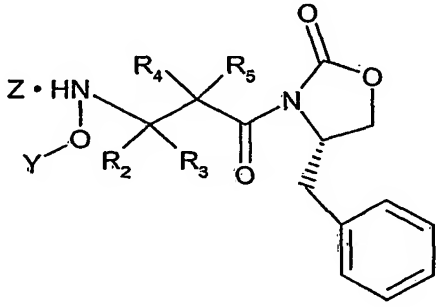
More specifically, the present invention is directed to a process for preparing a compound of the formula (VII)



(VII)

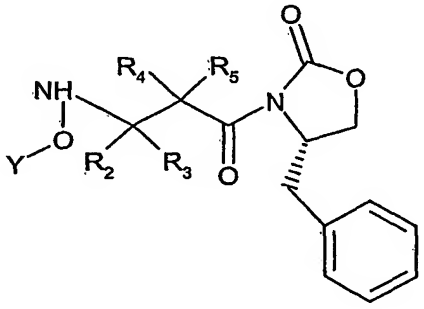
comprising Step 1A:

Contacting a compound of the formula (I)



(I)

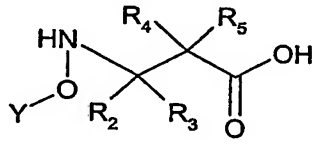
with a base in a suitable solvent to form the free base of compound (I), i.e., compound (II) of the formula (II)



(II)

followed by Step 1B:

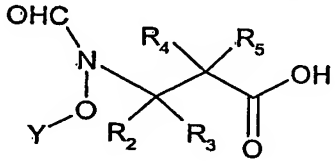
Contacting compound (II) with a strong nucleophile/weak base in a suitable solvent under conditions to form compound (III) of the formula (III)



(III)

followed by Step 2A:

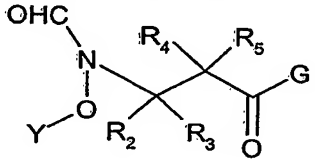
Contacting compound (III) with a formylating agent in a suitable solvent under conditions suitable to form a compound of formula (IV)



(IV)

followed by Step 2B:

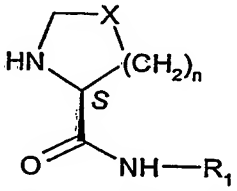
Contacting compound (IV) with an amine or an alkaline metal hydroxide in a suitable solvent under conditions to form a compound of formula (V)



(V)

followed by Step 3:

Contacting compound (V) with a compound of formula (VI)



(VI)

in the presence of a suitable base and one or more coupling agents in a suitable solvent under conditions to form a compound of formula (VII)

wherein

Y is a hydroxy protecting group;

Each of R_2, R_3, R_4 and R_5 is, independently, hydrogen or alkyl, or (R_2 and R_3) and/or (R_4 and R_5) collectively form a C_{4-7}cycloalkyl;

G is -$O^{\ominus}$metal$^{\oplus}$ or -OH•amine;

X is -CH_2-, -S-, -CH(OH)-, -CH(OR)-, -CH(SH)-, -CH(SR)-, -CF_2-, -C=N(OR)- or -CH(F)-; wherein

R is alkyl;

R_1 is aryl or heteroaryl;

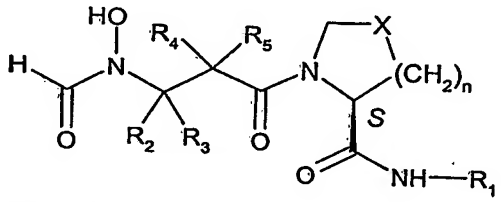
Z is a strong organic or inorganic acid; and

n is 0-3, provided that when n is 0, X is -CH_2-.

When the desired product is an N-oxide of an aromatic moiety having a nitrogen heteroatom (e.g., when R_1 is Formula X, Xa or Xb), typically a pyridine derivative, it is necessary to perform an additional step after step 3, i.e., to oxidize the N of the aromatic ring (Step 4). Therefore, the present invention includes Step 4 which comprises contacting the compound of formula VII, wherein R_1 is heteroaryl having an N heteroatom, with an oxidizing agent to form the corresponding N-oxide derivative.

In addition to the above process comprising Steps 1A-4 the present invention is directed to each of the steps individually, and to any two or more sequential steps.

In particular, the present invention provides a process for preparing intermediates useful in the preparation of a *N*-[1-oxo-2-alkyl-3-(*N*-hydroxyformamido)-propyl]-(carbonylamino-aryl or -heteroaryl)-azacyclo$_{4-7}$alkane or thiazacyclo$_{4-7}$alkane, e.g., a compound of formula (VIII)

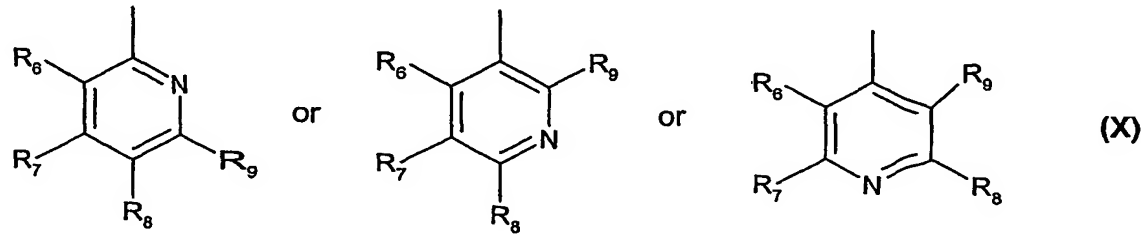


(VIII)

wherein R_1, R_2, R_3, R_4,R_5, X and n are as defined above.

To convert the compound of formula (VII) to the compound of formula (VIII), the hydroxy protecting group is removed using conventional hydrogenolysis techniques known in the art, e.g., by contacting the compound of formula (VII) with a palladium catalyst, such as Pd/$BaSO_4$ (see WO 02/102790 A1).

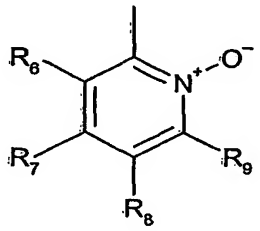
The R_1 moiety can be a heteroaryl, e.g., an azacyclo$_{4-7}$alkane, a thiazacyclo$_{4-7}$alkane or an imidazacyclo$_{4-7}$alkane. Specific examples of R_1 moieties in the compounds disclosed herein are heteroaryls of formula (X)



(X)

wherein each of R_6, R_7, R_8 and R_9, independently, is hydrogen, alkyl, substituted alkyl, hydroxy, alkoxy, acyl, acyloxy, SCN, halogen, cyano, nitro, thioalkoxy, phenyl, heteroalkylaryl, alkylsulfonyl or formyl.

A example of an R_1 moiety is a heteroaryl of formula (Xa)



(Xa)

wherein R_6, R_7, R_8 and R_9 are as defined above for formula (X), e.g.,

wherein

a) R_6 is nitro, alkyl, substituted alkyl, phenyl, hydroxy, formyl, heteroalkylaryl, alkoxy, acyl or acyloxy; preferably alkyl, especially C_{1-7}alkyl; hydroxyl; or alkoxy, especially a C_{1-7}alkoxy; and
R_7, R_8 and R_9 are hydrogen; or

b) R_6, R_8 and R_9 are hydrogen; and
R_7 is alkyl, substituted alkyl, phenyl, halogen, alkoxy or cyano, preferably alkyl, especially C_{1-7}alkyl; substituted alkyl, especially substituted C_{1-7}alkyl, such as $-CF_3$; or alkoxy, especially C_{1-7}alkoxy; or

c) R_6, R_7 and R_9 are hydrogen; and
R_8 is alkyl, substituted alkyl, halogen, nitro, cyano, thioalkoxy, acyloxy, phenyl, alkylsulfonyl or carboxyalkyl, preferably alkyl, especially C_{1-7}alkyl; substituted alkyl, especially $-CF_3$; halogen; or carboxyalkyl; or

d) R_6, R_7 and R_8 are hydrogen; and
R_9 is alkyl, halogen or hydroxy; or

e) R_7 and R_9 are hydrogen; and
each of R_6 and R_8, independently, is halogen, alkyl, substituted alkyl, phenyl or cyano; or

f) Each of R_7 and R_9 is alkyl or substituted alkyl; and
R_6 and R_8 are hydrogen; or

g) R_6 and R_9 are hydrogen;
R_7 is alkyl or substituted alkyl; and
R_8 is nitro; or

h) R_8 and R_9 are hydrogen;
R_6 is cyano; and
R_7 is alkoxy; or

i) R_7 and R_8 are hydrogen; and
R_6 is alkyl, substituted alkyl, alkoxy or SCN; and
R_9 is alkyl or substituted alkyl; or

j) R_6 and R_7 are hydrogen;
R_8 is nitro or halogen; and
R_9 is alkyl or substituted alkyl; or

k) R_6, R_7, R_8 and R_9 are hydrogen; or

l) R_6 and R_7 together with the carbon atoms to which they are attached form a phenyl group, preferably substituted with hydroxy; and
R_8 and R_9 are hydrogen; or

m) R_6 and R_7 are hydrogen; and
R_8 and R_9 together with the carbon atoms to which they are attached form a phenyl group; or

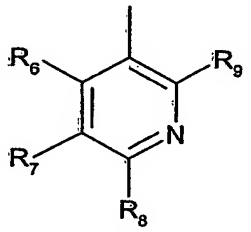
n) n is 0; or

o) n is 0;
each of R_6, R_7, R_8 and R_9, independently, is hydrogen, alkyl or halogen; and
more particularly, R_6, R_7, R_8 and R_9 are hydrogen; or

p) n is 0;
R_6, R_8 and R_9 are hydrogen; and
R_7 is alkyl; or

q) n is 0;
R_6, R_7 and R_9 are hydrogen; and
R_8 is alkyl or halogen.

In another embodiment, R_1 is of formula (Xb)



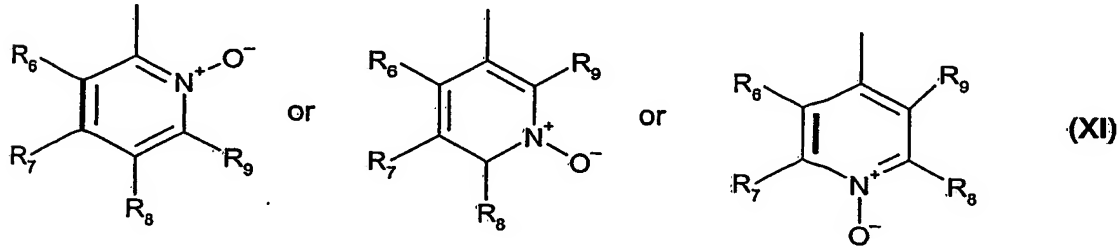
(Xb)

wherein

R_6, R_7, R_8 and R_9 are as defined above for formula (X); in particular, R_7 and R_8 together with the carbon atoms to which they are attached form a phenyl group; and

R_6 and R_9 are hydrogen.

In yet another embodiment, the R_1 is of formula (XI)



(XI)

wherein each of R_6, R_7, R_8 and R_9, independently, is hydrogen, alkyl, substituted alkyl, phenyl, halogen, hydroxy or alkoxy, e.g.,

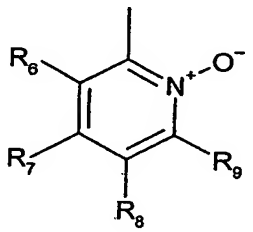
wherein

a) R_6 and R_8 are hydrogen;
R_9 is hydrogen or alkyl; and
R_7 is alkyl, substituted alkyl or phenyl; or

b) R_6, R_7 and R_9 are hydrogen; and
R_8 is halogen, alkyl or substituted alkyl; or

c) R_7, R_8 and R_9 are hydrogen; and
R_6 is hydroxy.

In a particularly useful embodiment the heteroaryl is of the formula (XIa)

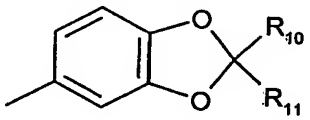


(XIa)

wherein R_6, R_7, R_8 and R_9 are as defined above for formula (XI).

In another embodiment, R_1 is an unsubstituted phenyl or the phenyl is substituted with alkoxy, e.g., methoxy; or aryloxy, e.g., phenoxy.

In another embodiment, the R_1 is of formula (XII)



(XII)

wherein each of R_{10} and R_{11}, independently, is hydrogen or halogen. In particular, R_{10} and R_{11} are both either hydrogen or both halogen.

Unless otherwise stated, the following terms as used in the specification have the following meaning.

The term "cycloalkane" or "cycloalkyl" contains from 3- to 7-ring carbon atoms, and is, e.g., cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term "azacyclo$_{4-7}$alkane" contains 1-ring heteroatom which is a nitrogen. It contains from 4-7, and especially 4- or 5-ring atoms including the heteroatom.

The term "thiazacyclo$_{4-7}$alkane" contains 2-ring heteroatoms, nitrogen and sulfur. It contains from 4-7, and especially 5-ring atoms including the heteroatoms.

The term "imidazacyclo$_{4-7}$alkane" contains 2-ring heteroatoms which are both nitrogen. It contains from 4-7, and especially 5-ring atoms including the heteroatoms.

The term "alkyl" refers to saturated or unsaturated aliphatic groups, such as alkenyl or alkynyl, cycloalkyl or substituted alkyl including straight-chain, branched-chain and cyclic groups having from 1-10 carbons atoms. Preferably "alkyl" or "alk", whenever it occurs, is a saturated aliphatic group or cycloalkyl, more preferably C_{1-7}alkyl, particularly C_{1-4}alkyl. Examples of "alkyl" or "alk" include, but are not limited to, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *t*-butyl, *n*-pentyl, neopentyl, *n*-hexyl or *n*-heptyl, cyclopropyl and especially *n*-butyl.

The term "substituted alkyl" refers to an alkyl group that is substituted with one or more substituents preferably 1-3 substituents including, but not limited to, substituents, such as halogen, lower alkoxy, hydroxy, mercapto, carboxy, cycloalkyl, aryl, heteroaryl and the like. Examples of substituted alkyl groups include, but are not limited to, $-CF_3$, $-CF_2-CF_3$, hydroxymethyl, 1- or 2-hydroxyethyl, methoxymethyl, 1- or 2-ethoxyethyl, carboxymethyl, 1- or 2-carboxyethyl and the like.

The term "aryl" or "Ar" refers to an aromatic carbocyclic group of 6-14 carbon atoms having a single ring including, but not limited to, groups, such as phenyl; or multiple condensed rings including, but not limited to, groups, such as naphthyl or anthryl; and is especially phenyl.

The term "heteroaryl" or "HetAr" refers to a 4- to 7-membered, monocyclic aromatic heterocycle or a bicycle that is composed of a 4- to 7-membered, monocyclic aromatic heterocycle and a fused-on benzene ring. The heteroaryl has at least one hetero atom, preferably one or two heteroatoms including, but not limited to, heteroatoms, such as N, O and S, within the ring. A preferred heteroaryl group is pyridinyl, pyrimidinyl or benzdioxolanyl.

The aryl or heteroaryl may be unsubstituted or substituted by one or more substituents including, but not limited to, C_{1-7}alkyl, particularly C_{1-4}alkyl, such as methyl, hydroxy, alkoxy, acyl, acyloxy, SCN, halogen, cyano, nitro, thioalkoxy, phenyl, heteroalkylaryl, alkylsulfonyl and formyl.

The term "carbonylamine", as used herein, refers to a -NHC(O)- group wherein the amino portion of the group is linked to the aryl/heteroaryl and the carbonyl portion of the group is linked to the azacyclo$_{4-7}$alkane, thiazacyclo$_{4-7}$alkane or imidazacyclo$_{4-7}$alkane.

The term "heteroalkyl" refers to saturated or unsaturated C_{1-10}alkyl as defined above, and especially C_{1-4}heteroalkyl which contain one or more heteroatoms, as part of the main, branched or cyclic chains in the group. Heteroatoms may independently be selected from the group consisting of -NR-, where R is hydrogen or alkyl, -S-, -O- and -P-; preferably -NR-, where R is hydrogen or alkyl; and/or -O-. Heteroalkyl groups may be attached to the remainder of the molecule either at a heteroatom (if a valence is available) or at a carbon atom. Examples of heteroalkyl groups include, but are not limited to, groups, such as -O-CH_3, -CH_2-O-CH_3, -CH_2-CH_2-O-CH_3, -S-CH_2-CH_2-CH_3, -CH_2-CH(CH_3)-S-CH_3 and -CH_2-CH_2-NH-CH_2-CH_2-.

The heteroalkyl group may be unsubstituted or substituted with one or more substituents, preferably 1-3 substituents including, but not limited to, alkyl, halogen, alkoxy, hydroxyl, mercapto, carboxy and, especially, phenyl. The heteroatom(s) as well as the carbon atoms of the group may be substituted. The heteroatom(s) may also be in oxidized form.

The term "alkoxy", as used herein, refers to a C_{1-10}alkyl linked to an oxygen atom, or preferably C_{1-7}alkoxy, more preferably C_{1-4}alkoxy. Examples of alkoxy groups include, but are not limited to, groups, such as methoxy, ethoxy, *n*-butoxy, *tert*-butoxy and allyloxy.

The term "acyl", as used herein, refers to the group -(O)CR, where R is alkyl, especially C_{1-7}alkyl, such as methyl. Examples of acyl groups include, but are not limited to, acetyl, propanoyl and butanoyl.

The term "acyloxy", as used herein, refers to the group -OC(O)R, wherein R is hydrogen, alkyl, especially C_{1-7}alkyl, such as methyl or ethyl, or phenyl or substituted alkyl as defined above.

The term "alkoxycarbonyl", as used herein, refers to the group -COOR, wherein R is alkyl, especially, C_{1-7}alkyl, such as methyl or ethyl.

The term "halogen" or "halo", as used herein, refers to chlorine, bromine, fluorine, iodine and, is especially, fluorine.

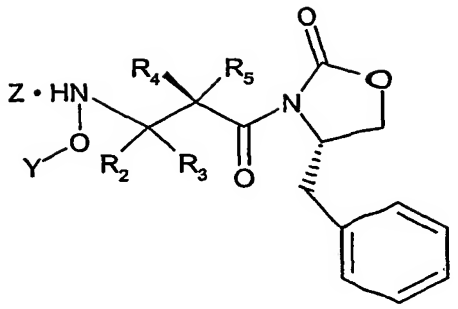
The term "thioalkoxy", as used herein, means a group -SR, where R is an alkyl as defined above, e.g., methylthio, ethylthio, propylthio, butylthio and the like.

The term "heteroalkylaryl", as used herein, means a heteroalkyl group, e.g., -O-CH_2- substituted with an aryl group, especially, phenyl. The phenyl group itself may also be substituted with one or more substituents, such as halogen, especially, fluoro and chloro; and alkoxy, such as methoxy.

The term "alkylsulfonyl", as used herein, means a group -SO_2R, wherein R is alkyl, especially, C_{1-7}alkyl, such as methyl sulfonyl.

"Protecting group" refers to a chemical group that exhibits the following characteristics: 1) reacts selectively with the desired functionality in good yield to give a protected substrate that is stable to the projected reactions for which protection is desired; 2) is selectively removable from the protected substrate to yield the desired functionality; and 3) is removable in good yield by reagents compatible with the other functional group(s) present or generated in such projected reactions. Examples of suitable protecting groups may be found in Greene et al., *Protective Groups in Organic Synthesis*, 3rd Edition, John Wiley & Sons, Inc., NY (1999). Preferred hydroxy protecting groups include benzyl, Fmoc, TBDMS, photolabile protecting groups, such as Nvom, Mom and Mem. Other preferred protecting groups include NPEOC and NPEOM.

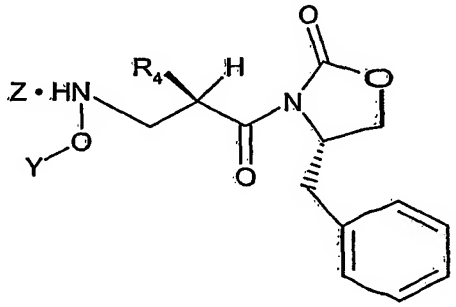
It will be appreciated that the compounds disclosed herein may exist in the form of optical isomers, racemates or diastereoisomers. In particular, in the compounds disclosed herein where R_4 and R_5 are different, the carbon atom to which the R_4 and R_5 groups are bonded is a chiral center and such compounds can exist in the *R*, *S* or racemic forms. It is contemplated that the process of the invention prepares the *R* optically pure form. By "optically pure" is meant that the enantiomeric purity is greater than 50%, preferably greater than 80%, more preferably greater than 90%, and most preferably greater than 95%. The optically pure *R* isomer of compound (I) can be used, in which case all subsequent compounds in the synthesis will remain in the *R* optically pure form, with respect to the same chiral carbon atom. Such *R* form of compound (I) is represented by former Ia below:



(Ia)

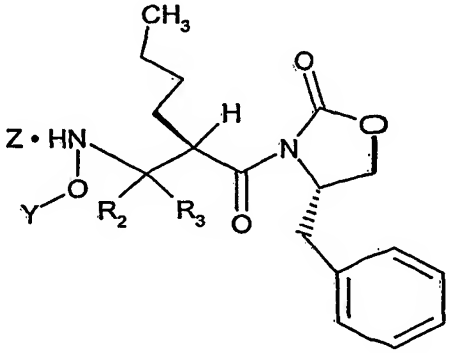
wherein R_2, R_3, R_4 and R_5 are as defined above. It is exemplified that in the compound of formula (I) that R_5 is hydrogen and that R_4 is C_{2-10}alkyl, more preferably C_{2-7}alkyl, and most preferably C_4alkyl.

It is further exemplified that in the optically pure compound of formula (I) that R_2, R_3, and R_5 are hydrogen and that R_4 is alkyl; such a compound has the structure (Ib)



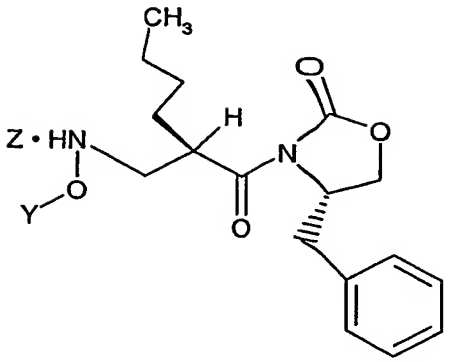
(Ib)

As an example, in compound (I), R_4 is *n*-butyl, where such compound has the structure (Ic)



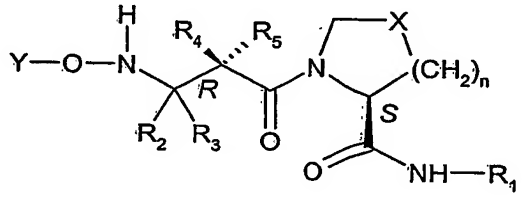
(Ic)

Further exemplified is that R_2, R_3 and R_5 are hydrogen and that R_4 is *n*-butyl; such compound has the structure (Id)



(Id)

Alternatively, the racemate form of compound (I) can be used and then the *R* form can be resolved at a later step and the *R* form used for subsequent steps. For example, the compound formed after Step 3 or 3A, can be resolved into its *RS* and *SS* diastereomers and only the *RS* diastereomer used for subsequent steps. The *RS* diastereomer of compound (VII) is depicted below or formula (VIIa):



(VIIa)

wherein R_2, R_3, R_4 R_5 Y, X, R_1 and n are as defined above, provided that R_4 and R_5 are different.

The optical isomers are resolved using standard techniques known in the art, for example, using silica gel column chromatography and an ethyl acetate/hexane solvent system. See, e.g., the methods taught in Chapter 4 of *Advanced Organic Chemistry*, 4th Edition, March, John Wiley and Sons, NY (1992).

In the compounds disclosed herein, the following significances are exemplefied individually or in any sub-combination:

1. R_1 is a heteroaryl of formula (Xa),
   wherein
   R_6, R_7 and R_9 are hydrogen and R_8 is methyl or trifluoromethyl; or
   R_6, R_7 and R_9 are hydrogen and R_8 is fluoro; or
   R_6, R_7 and R_8 are hydrogen and R_9 is fluoro; or

R_6, R_8 and R_9 are hydrogen and R_7 is ethyl or methoxy; or

R_7, R_8 and R_9 are hydrogen and R_6 is hydroxy; or

R_7 and R_8 are hydrogen, R_6 is methoxy and R_9 is methyl; or

R_1 is a heteroaryl of formula (Xb),

wherein

R_6, R_7 and R_9 are hydrogen and R_8 is fluoro or trifluoromethyl; or

R_6, R_8 and R_9 are hydrogen and R_7 is ethyl; preferably R_1 is a heteroaryl of formula (Xa),

wherein R_6, R_8 and R_9 are hydrogen and R_7 is ethyl or a heteroaryl of formula (Xb),

wherein R_6, R_7 and R_9 are hydrogen and R_8 is fluoro.

2. X is $-CH_2-$, -CH(OH)-, -CH(OR)-, $-CF_2-$ or -CH(F)-, preferably X is $-CH_2-$;
3. R_4 is alkyl, preferably C_{1-7}alkyl, such as *n*-butyl;
4. n is 1.

Temperature and pressure are not known to be critical for carrying out any of the steps of the invention, i.e., Steps 1A-4. Generally, for any of the steps, a temperature of about -10°C to about 150°C, typically about 0°C to about 80°C, is employed. Typically about atmospheric pressure is used for convenience; however, variations to atmospheric pressure are not known to be detrimental. Oxygen is not known to be detrimental to the process, therefore for convenience the various steps can be performed under ambient air, although an inert atmosphere, such as nitrogen or argon, can be used if desired. For convenience equimolar amounts of reactants or reagents, as appropriate, are typically used; however molar ratios can vary from about 1 to 2 equivalents, relative to the other reactant/reagent. The pH for the various steps is typically about 2 to about 12. The solvent used for the various steps are typically organic solvents, although in some situations aqueous/organic solvents can be used. Examples of suitable solvents include dioxane; methylene chloride; dichloromethane; toluene, acetone; methyl ethyl ketone; THF; isopropyl acetate; DMF; alcohols, especially, ethyl acetate, acetonitrile, higher-branched alcohols, such as *t*-butanol; and the like.

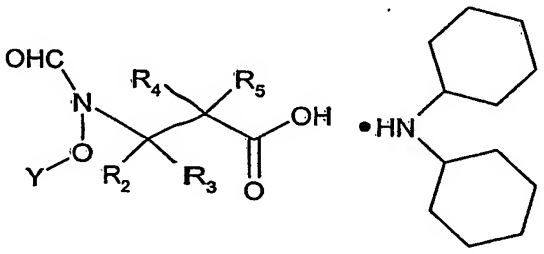
For Step 1A, a typical temperature is about 10°C to about 40°C, more typically about 15°C to about 25°C; and a typical reaction time is about 0.1 hours to about 3 hours, more typically about 0.25 hours to about 1 hour. A pH of about 6 pH to about 10 pH, typically about 8 pH to about 9 pH, more typically about 9 pH, is employed. The base for Step 1A is a water soluble base such as sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, an alkaline metal hydroxide, e.g., sodium hydroxide, potassium hydroxide, and the like. The solvent for Step 1A is a biphasic solvent, i.e., a mixture of water and an organic solvent immicible with water, for example, ethyl acetate, methylene chloride, diethyl ether, methyl *t*-butyl ether, isopropyl acetate, and the like. An example of a solvent is water/ethyl acetate. To prepare the starting compound of formula (I) for Step 1A (i.e., a salt) a strong acid is added to the corresponding free amine in solution with an organic solvent such as ethyl acetate, ethyl ether, and the like. The Z substituent, i.e., the strong acid, must be of sufficient strength to form a salt of the amine which results in the compound of formula (I) precipitating from the organic solution. The Z substituent is a strong organic or inorganic acid such as HCl, HBr, benzenesulfonic acid, toluenesulfonic acid, camphorsulfonic acid, and the like.

For Step 1B, a typical temperature is about -10°C to about 10°C, more typically about -3°C to about 2°C; and a typical reaction time is about 0.5 hours to about 5 hours more typically about 0.75 hours to about 1.5 hours. The pH for Step B is typically about 8 pH to about 11 pH. The strong nucleophile/weak base used in Step 1B can be, for example, lithium hydroperoxide or a thiolate salt of an alkaline metal such as the sodium salt of propanethiol. The strong nucleophile/weak base is typically formed *in situ*, such as by adding hydrogen peroxide and an alkaline metal hydroxide, for example adding hydrogen peroxide and lithium peroxide to form lithium hydroperoxide *in situ*. The solvent for Step 2A can be a mixture of water and an ether solvent that is water miscible, such as THF, dimethylethane, dioxane, and the like. A typical solvent is THF/water.

For Step 2A, a typical temperature is about -20°C to about 20°C, more typically about -10°C to about 5 °C; and a typical reaction time is about 0.25 hours to about 2 hours, more typically about 0.3 hours to about 1 hour. The pH for Step 2A is typically, about 1 pH to about 6 pH. The formylating agent for Step 2A is typically formed *in situ*, such as by adding formic acid and acetic anhydride to form formic acetic anhydride. The solvent for Step 2A is an inert solvent in which the desired compound is soluble, for example, ethyl acetate,

isopropyl acetate, methyl acetate, n-butyl acetate and the like. A typical solvent is ethyl acetate.

For Step 2B, a typical temperature is about -5°C to about 40°C, more typically about 15°C to about 25°C; and a typical reaction time is about 1 hour to about 5 hours, more typically about 2 hours to about 3 hours. The pH for Step 2B is typically about 1 pH to about 6 pH. Typical solvents fro Step 2B include ethyl acetate, iso-propyl acetate, , heptane, and the like. A particular example of a solvent is heptane. Examples of G substituents include - $O^{\ominus}metal^{\oplus}$ wherein the metal is Na, K, Mg, Li, or -OH•amine wherein the amine of the formula HNR'R', wherein each R' is a straight chain, branched chain or cyclo alkyl group of 1 to 8 carbon atoms, more typically 1 to 6 carbon atoms. A typical example of a G substituent is -OH•amine wherein the amine is dicyclohexylamine. Therefore, an example of the compound of formula (V) has the structure:



(V)

For Step 3, a typical temperature is about 10°C to about 40°C, more typically about 15°C to about 25°C; and a typical reaction time is about 5 minutes to about 15 hours, more typically about 10 minutes to about 10 hours. The pH for Step 3 is typically about 5 to about 9. The solvent for Step 3 is a biphasic solvent, i.e., a mixture of water and an organic solvent immicible with water, for example, ethyl acetate, methylene chloride, diethyl ether, methyl *t*-butyl ether, isopropyl acetate, and the like. A typical solvent is water/ethyl acetate. Typical bases for Step 3 include tertiary amine bases such as N-methylmorphylene, triethyl amine, diisopropylethylamine, and the like. The coupling agent can be a conventional coupling agent known in the art, for example as disclosed in J. Jones, "The Chemical Synthesis of Peptides", Clarendon, Oxford, 1991 ans P. Lloyd Williams, F. Albericio and E. Girault, Tetrahedron, !993, 49, 11065, incorporated herein by reference. One or more coupling agents are used. Examples of coupling agents include EDCI, HOBt, DCC, HATU,

BOP, FDPP, cross linked enzyme crystals such as PEPTI CLEC-TR, and the like. A typical coupling agent is EDCI/HOBt. A typical molar ration of DCCI:HOBt is about 1:5 to about 5:1.

For Step 4, a typical temperature is about 10°C to about 35°C, more typically about 20°C to about 22°C; and a typical reaction time is about 60 minutes to about 18 hours, more typically about 4 hours to about 8 hours. The pH for Step 4 is typically about 4 to about 8. The solvent for Step 4 is typically an organic solvent, i.e., ethyl acetate, iso–propyl acetate, methylene chloride, and the like. The oxidizing agent can be a conventional agent known in the art, for example as disclosed in March, "Advanced Organic Chemistry", 5th Ed., Wiley Interscience, NY, Chapter 19, incorporated herein by reference. Typical oxidizing agents include urea/hydrogen peroxide with phthalic anhydride; magnesium monoperoxyphthalate; MCPBA, Oxone (available from Aldrich), and the like.

Insofar as the production of starting materials is not particularly described, the compounds are known or may be prepared analogously to methods known in the art or as disclosed in the examples hereinafter.

The following abbreviations are used:

Ac = acetyl

BOP = [benzotriazol-1–yloxytris(dimethylamino)phosphonium hexafluorophosphate

CDMT = chlorodimethoxy triazine

DIEA = diisopropylethylamine

DCC = dicyclohexylcarbodimide

DMF = dimethylformamide

EDCI = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride

2-EHA = 2-ethylhexanoic acid

EtOAc = ethyl acetate

EtOH = ethanol

HATU = [O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate]

isobutyl chloroformate

HPLC = high performance liquid chromatography

MCPBA = metachloroperoxybenzoic acid

MeOH = methanol

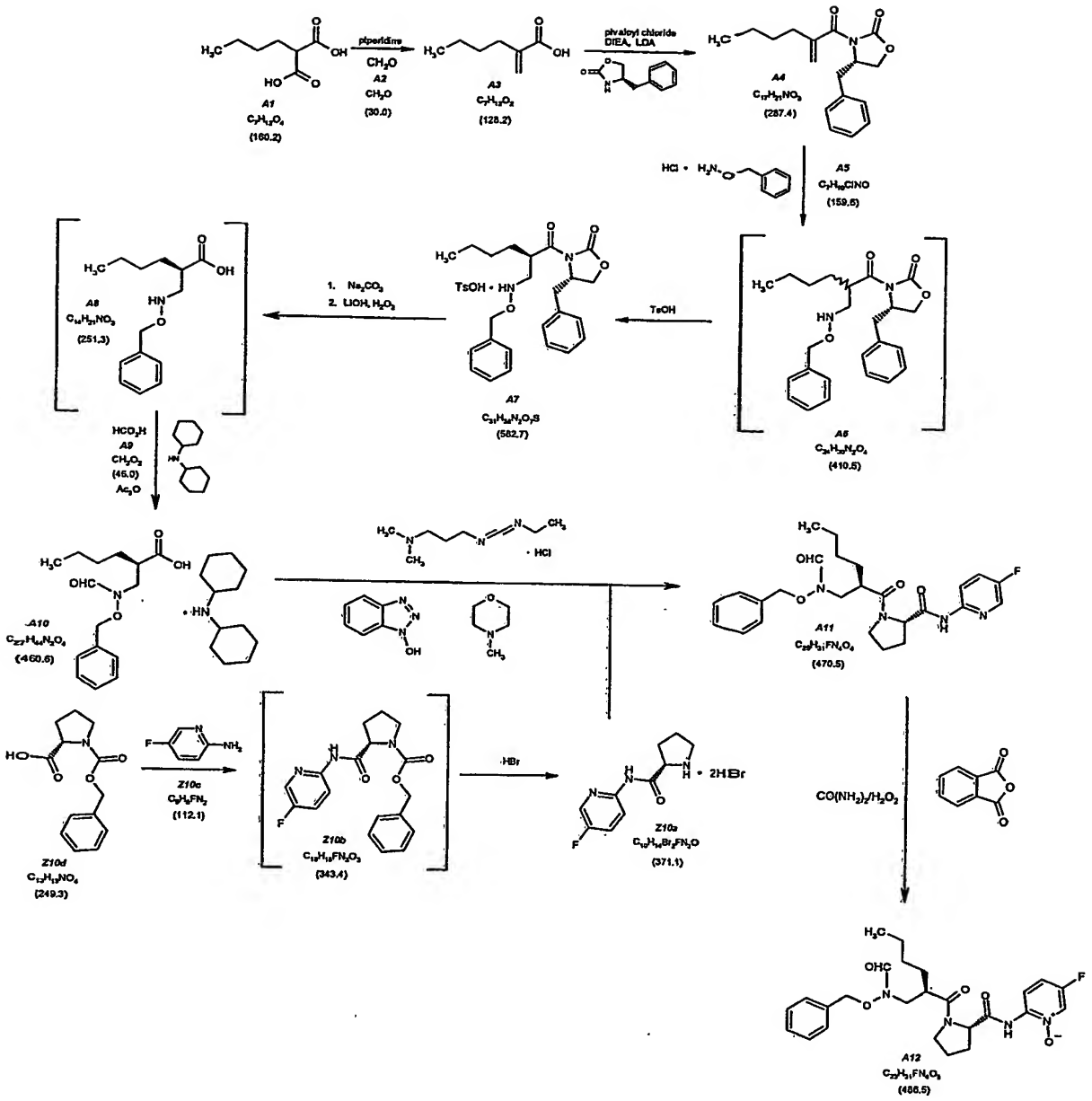
MMPP = magnesium monoperoxyphthalate

RT = room temperature
THF = tetrahydrofuran

The following illustrates a preferred process of the invention.

Reaction Scheme

The following examples illustrate the invention but should not be interpreted as a limitation thereon. Product numbers refer to the preferred reaction scheme depicted immediately below.



General procedure for the synthesis of intermediates useful for the preparation of:

(2*S*)-*N*-(5-fluoro-1-oxido-2-pyridinyl-1-[(2*R*)-2-[formylhydroxyamino)methyl]-1-oxohexyl]-2-pyrrolidinecarboxamide, magnesium salt

Step 1: (2*R*)-2-[[(phenylmethoxy)amino]methyl]-hexanoic acid (A8)

To a solution of the *p*-TSA salt (**A7**) (58.3 g, 0.1 mol) in ethyl acetate (200 mL) and water (50 mL) was added 1 N Na_2CO_3 (185 mL). The two phase mixture was stirred for 15 minutes at RT and the lower aqueous layer was separated. The organic layer was washed with water (2 x 50 mL), and concentrated to give the free base of **A7**.

The **A7** free base (41.0 g, 0.1 mol) was dissolved in THF (395 mL) and water (107 mL) and cooled to -3°C. To this solution was added 30% hydrogen peroxide (26.1 g, 0.23 mol) keeping the temperature at -3°C. In a separate flask, a solution of lithium hydroxide (5.0 g, 0.12 mol) in water (107 mL) was prepared and added slowly to the **A7**/hydrogen peroxide solution keeping the temperature at -3°C. The mixture was stirred for 45 minutes at this temperature.

A solution of sodium sulfite (43.5 g, 0.345 mol) in water (855 mL) was added slowly keeping the temperature below 10°C and the reaction mixture was allowed to warm to RT. The solution was partially concentrated under vacuum to remove the THF and the aqueous portion was extracted with ethyl acetate (6 x 110 mL). The aqueous portion was then acidified with 3 N HCl (78 mL) and extracted with ethyl acetate (2 x 215 mL). The ethyl acetate extracts were combined and washed with water (2 x 110 mL). The organic solution was partially concentrated under vacuum (200 mL) to give a colorless solution of **A8** which was used as is in the following step.

A sample was concentrated completely for characterization.

1H NMR ($CDCl_3$): δ 7.4 (s, 5H), 6.85 (bs, 2H), 4.75 (dd, 2H), 3.1 (m, 2H), 2.8 (m, 1H), 2.7 (m, 1H), 2.55 (m, 1H),1.2 (m, 4H), 0.88 (m, 3H). ES-MS: calcd. for $C_{14}H_{21}NO_3$ (251.3); found: 252.2 [M+H].

Step 2: (*2R*)-2-[[formyl(phenylmethoxy)amino]methyl]-hexanoic acid dicyclohexylamine salt (**A10**)

Acetic anhydride (15.3 g, 0.15 mol) was cooled to 0-5°C and treated with 96% formic acid (27.6 g, 0.6 mol) keeping the temperature below 10°C. The mixture was stirred for 15 minutes at 0-5°C and then warmed to RT and stirred for 15 minutes more.

In a second flask, **A8** ethyl acetate solution (502 g, 0.75 mol) was cooled to -15°C and the formic acid/acetic anhydride mixture was added to it keeping the temperature at -10 ± 5°C. The reaction mixture was stirred for 20 minutes at this temperature and then water (5.4 g) was added. After stirring for 15 minutes, the solution was warmed to RT. The solution was

concentrated under vacuum (final volume = 70-90 mL). Toluene (240 mL) was added and the solution was again concentrated under vacuum (final volume = 70-80 mL).

In a separate flask a mixture of dicyclohexylamine (16.3 g) in heptane (240 mL) was prepared and this was added to the concentrate at RT. The mixture was seeded and held with stirring for 2 hours. Heptane (145 mL) was added and the suspension was held for 8 hours at RT. The solids were isolated by filtration and dried under vacuum to give the title compound.

m.p.: 83-86°C; *1H* NMR ($CDCl_3$, rotamers): δ 8.05 (bd, 1H), 7.3-7.65 (m, 5H), 4.75–5.1 (m, 2H), 3.5-4.0 (m, 2), 3.1-3.39 (m, 1H), 2.9 (m, 3H), 2.65 (m, 1H), 1.0-2.15 (m, 26H), 0.9 (s, 3H). ES-MS: calcd. for C15H21NO4 (free acid) (279); found: 280.1 [M+H].

Step 3: (2*S*)-*N*-(5-fluoro-2-pyridinyl)-1-[(2*R*)-2-[[formyl(phenylmethoxy)amino]methyl]-1-oxohexyl]-2-pyrrolidinecarboxamide (**A11**)

A solution of **A10** (34.55 g, 75 mmol) in ethyl acetate (300 mL) was mixed with a citric acid solution (30 g of citric acid in 270 mL of water) and stirred at RT for 10 minutes. The layers were separated and the upper organic layer was washed with water (2 x 225 mL). At this point, *N*-(5-fluoro-2-pyridinyl)-(2*S*)-2-pyrrolidinecarboxamide dihydrobromide (33.39 g, 90 mmol) was added followed by water (60 mL) and HOBt (12.81 g, 82.5 mmol).

The mixture was cooled to 0-5°C and EDCI (40.26 g, 210 mmol) and water (60 mL) were added. This was followed by the addition of N-methylmorpholine (47.79 g, 472.5 mmol). The reaction was stirred at RT overnight.

The lower aqueous layer was separated and the upper organic layer was washed with water (4 x 225 mL). The organic layer was filtered through a column of silica gel (83.4 g) and the column was further eluted with an additional volume of ethyl acetate (3 x 41 mL). The suitable fractions were combined and concentrated under vacuum to a specific volume (225 mL).

This solution was warmed to 50°C and treated with heptane (675 mL). The solution was then cooled to 45°C and seeded. The slurry was cooled to below -10°C and held for 2 hours. The solids were isolated by filtration and dried under vacuum to give the title compound.

m.p.: 98°C; *1H* NMR (DMSO, rotamers): δ 10.6, 10.8 (s, 1H), 8.2 (s, 1H), 7.5-8.2 (m, 3H), 6.95-7.4 (m, 5H), 4.8 (s, 2H), 4.55 (bs, 1H), 3.2-3.8 (m, 4H), 2.9 (bs, 1H), 1.6-2.4 (m, 4H), 1.0-1.55 (m, 6H), 0.8 (s, 3H) . ES-MS: calcd. for $C_{25}H_{31}FN_4O_4$ (470.6); found: 471.2 [M+H], 493.2 [M+Na].

Step 4: (2*S*)-*N*-(5-fluoro-1-oxido-2-pyridinyl)-1-[(2*R*)-2-[[formyl(phenylmethoxy)amino]methyl]-1-oxohexyl]-2-pyrrolidinecarboxamide (**A12**)

A mixture of magnesium monoperoxyphthalate (69.25 g, 140 mmol) in water (128 mL) and isopropyl acetate (300 mL) was stirred and a solution of **A11** (32.94 g, 70 mmol) in isopropyl acetate (162 mL) was added. The mixture was stirred for 17 hours at RT.

The bottom aqueous layer was separated and a solution of sodium sulfite (8.82 g, 70 mmol) in water (160 mL) was added. After stirring for 20 minutes, the bottom aqueous layer was separated and sodium carbonate (20 g, 190 mmol) in water (300 mL) was added. After stirring for 20 minutes, the bottom aqueous layer was separated and a solution of sodium chloride (19.0 g) in water (131 mL) was added. The layers were separated and the organic layer was concentrated under vacuum to a final volume of 92 mL.

The solution was filtered and the filtrate was heated to 40°C and heptane (80 mL) was added. The solution was allowed to slowly cool to 30°C and seed crystals were added. The mixture was held for one hour at this temperature and then cooled to 22°C and more heptane was added (545 mL). After all of the heptane was added, the suspension was held at 22°C for 2 hours and then further cooled to below -10°C and held for 1 hour. The solids were isolated by filtration and dried under vacuum to give the title compound.

m.p.: 70°C; *1H* NMR ($CDCl_3$, rotamers): δ 10.35 (s, 1H), 8.45-8.75 (m, 1H), 7.61-8.45 (m, 2H), 7.35 (s, 5H), 7.05 (s, 1H), 4.65-5.22 (m, 2H), 4.1-4.65 (m, 1H), 3.25-4.1 (m, 3.5H), 2.64-3.2 (m, 1.5H), 1.02-2.42 (m, 10H), 0.85 (s, 3H). ES-MS: calcd. for $C_{25}H_{31}FN_4O_5$ (486.5); found: 487.2 [M+H].